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TITLE: A National Coordinating Center for Prehospital Trauma Research Funding Transfusion Using Stored Fresh Whole Blood

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14. ABSTRACT Resuscitation protocols for trauma patients presenting with significant bleeding utilize administration of components of blood including RBCs, plasma, and platelets. Despite improvements in emergency surgery and critical care, trauma patients with severe bleeding still suffer from high incidence of complications and death compared to patients that require fewer or no transfusions. Recent studies from military centers indicate that transfusion of FWB may be more beneficial than individual blood components in patients with severe hemorrhage. This has not been studied in civilian trauma patients mainly due to the technical difficulties and costs. We propose a feasibility and hospital outcomes study using FWB (storage time of 5 days) for resuscitating trauma patients with significant bleeding. A cohort of adult trauma patients presenting with severe hemorrhage and receiving resuscitation with FWB will be prospectively compared to a control group of patients receiving standard component therapy. The shelf-life of whole blood, cost of treatment, levels of clotting and inflammatory markers in patient's blood samples, as well as the incidence of persistent bleeding, development of blood clots, infections, and mortality will be compared between the two groups. This study is designed to determine whether FWB transfusions are feasible in a civilian trauma center and to determine whether resuscitation using FWB is superior to component therapy in patients with severe hemorrhage.

15. SUBJECT TERMS

None listed.

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Introduction:

The National Trauma Institute (NTI) proposed to utilize $499,995 in Joint Warfighter Medical Research Program Funding to extend the work previously completed looking at the use of fresh whole blood (FWB) and its ability to be used for resuscitation. Hemorrhagic shock remains a major cause of potentially preventable death with common consequences including persistence and exacerbation of uncontrollable bleeding from refractory coagulopathy leading to early death from exsanguination. The Principal Investigator's preliminary data show that if whole blood is leukocyte reduced with a platelet sparing filter, it would be an acceptable standalone product for resuscitation from hemorrhagic shock that can be stored for prolonged periods of time. The aims for this funding are to 1) Determine the shelf life of whole blood units leukocyte reduced with a platelet sparing filter stored at 4 degrees; 2) prospectively determine the effectiveness of whole blood leukocyte reduced with a platelet sparing filter compared to component therapy as measured by coagulation capacity after transfusion and clinical outcomes; and 3) determine the feasibility of providing an inventory of whole blood leukoreduced with a platelet sparing filter for resuscitation of trauma patients in hemorrhagic shock.

Keywords:

Fresh Whole Blood; TEG; EFIC; resuscitation; platelets; leukoreduction, coagulation

Accomplishments:

The major goals of this project as identified in the Statement of Work are below with percent completion determinations and completion dates as appropriate.

Aims and Major Goals	Timeline in Months	Completion date	% Complete
Specific Aim 1: Determine the shelf life of whole blood Months			
Collection of whole blood units	1-9		0%
Testing of whole blood units for coagulation markers	1-9		0%
Analysis of in vitro study data	6-12		0%
Specific Aim 2: Determine the effectiveness of whole blood compared to component therapy			
Enrollment of trauma patients into the control arm, consisting of component therapy resuscitation	13-30		0%
Collection of whole blood units from volunteer blood donors	19-30		0%
Enrollment of trauma patients into the intervention group	19-30		0%
Blood sample collection from trauma patients	13-30		0%
Testing of blood samples from trauma patients	13-30		0%
Review of unexpected or adverse events by the medical monitor	13-30		0%
Data analysis	13-33		0%
Specific Aim 3: Determine the feasibility of providing whole blood for resuscitation of hemorrhagic shock			

Collection of data regarding whole blood utilization and cost	13-27		5%
Complete blood bank data base	28-30		5%
Analyze blood bank data base	28-33		0%
Other Major Tasks:			
Identification of communities in the UCLA catchment area	1-3		N/A
Advertisements for community meetings and focus groups	1-6		N/A
Hold community meetings and focus groups	3-6		N/A
IRB approval for Exemption from Informed Consent	4-9		N/A
Secretary General of the Army approval for Exemption from Informed Consent	7-18		N/A
Finalize consent form & human subjects protocol	10-12	IRB:8/10/16	80%
Submit amendments, adverse events, and protocol deviations	As needed	Ongoing	100%
IRB continuing review	Annually	6/27/17	100%
Research group meeting	Quarterly	8/25/17	100%

During this reporting period, the study PI has ensured that all regulatory/safety requirements were met, renewed the IRB application and certification of the laboratory space, and identified/delegated personnel to complete the project. All laboratory supplies to complete the clinical and laboratory portions of the study have been purchased and testing of the workflow to evaluate patients for coagulopathy in real-time is underway. The Blood Bank has identified a pool of whole blood donors and incorporated the new product (FWB) in terms of packaging and ordering/billing through the electronic health record. The study team has collaborated with all disciplines involved in this study (Blood Bank, Emergency Room, Trauma, Operating Room, Intensive Care Unit, etc) to coordinate and streamline standard operating procedures for the clinical portion of the study. Study packets have been designed to minimize the impact on workflow in all patient locations. A secure database has been designed to store clinical research data, and test data are being uploaded into the system and analyzed as a test of the procedure.

This project provides training for a research resident, Anaar Siletz, MD, in clinical trial design and management as well as training to student research assistants within the Emergency Medicine Research Associate program who will assist in identifying patients and collecting data.

Plans for the next quarterly reporting period include receiving HRPO approval of the change in the protocol, initiation of Aim 1 activities (the determination of the shelf life of whole blood), and enrollment of patients for aim 2 is anticipated to begin.

Impact:

The project has already led to a change in practice allowing whole blood for transfusion of male trauma patients at UCLA (the clinical site).

The change in practice affects surgical, emergency department, and critical care disciplines as well as blood product management.

There is no impact on technology transfer or on society beyond science and technology at this time.

Changes/Problems:

An FDA Approval for IND exemption was obtained (official notice of approval received 5/25/17). During the FDA review, the following changes were made to the protocol:

1. A staged approach to transfusing whole blood will be used. The first 10 patients enrolled will receive up to 4 units of whole blood. The UCLA Transfusion Committee will then review clinical data on these patients to ensure no adverse outcomes suggesting increased risk of hemolysis or platelet dysfunction prior to approving up to 5 units of whole blood transfusion. After 10 patients have received up to 5 units of whole blood, the Transfusion Committee will again review the data before approving transfusion of up to 6 units of whole blood.

2. To facilitate comparison with prior studies, the primary endpoint of the study will be volume of blood products transfused in the first 24 hours of admission. Thromboelastography data will be collected as secondary endpoints. Otherwise, endpoints are unchanged.

The study was delayed while obtaining a formal IND exemption from the FDA. Based on the changes to the protocol made under FDA advisement (see above) the protocol was resubmitted to HRPO and is awaiting approval. However, all personnel and procedures are ready to begin once HRPO approval is obtained.

Possible reasons for delay once HRPO approval is obtained include longer-than-anticipated time required to incorporate use of whole blood into blood bank procedures. In this case, the clinical site will run the study protocol using the usual component therapy which will contribute to the control group data. Data for historic controls will also be collected during this time.

Products:

There have been no products as a result of this project at this time.

Participants:

Name	Project Role	Nearest person month worked	% Effort	Contribution to the project
Donald Jenkins	Principal Investigator	0.6	5%	Oversight of entire project
Roy Estrada	Program Manager	0.18	8%	Regulatory oversight and coordination of reviews and reporting from site to NTI and from NTI to MRMC

Amy Flores	Controller	0.6	5%	Managed financial operations for this study at NTI and at the clinical site
Michelle Price	Program Manager	0.25	2.5%	Regulatory oversight and coordination of reviews and reporting from site to NTI and from NTI to MRMC
Monica Phillips	Director of Finance	0.03	2%	Executed and managed subaward

There were changes in personnel due to staff changes at NTI. Roy Estrada worked on this project at 8% for 1.5 months. He was replaced by Michelle Price at 2.5%. Monica Phillips worked on this project at 2% for 1.5 months. After 1.5 months of training, her role was filled by Amy Flores who worked on this project at 5% for the entire year.

The University of California Los Angeles is collaborating and actually performing the study. They are a subaward recipient to this grant.

Special Reporting:

Quad Chart: The Quad Chart for this grant is attached as appendix A.

Transfusion of Stored Fresh Whole Blood in a Civilian Trauma Center: A Prospective Evaluation of Feasibility and Outcomes

ERMS/Log Number: JW140027

Award Number: W81XWH-15-2-0039

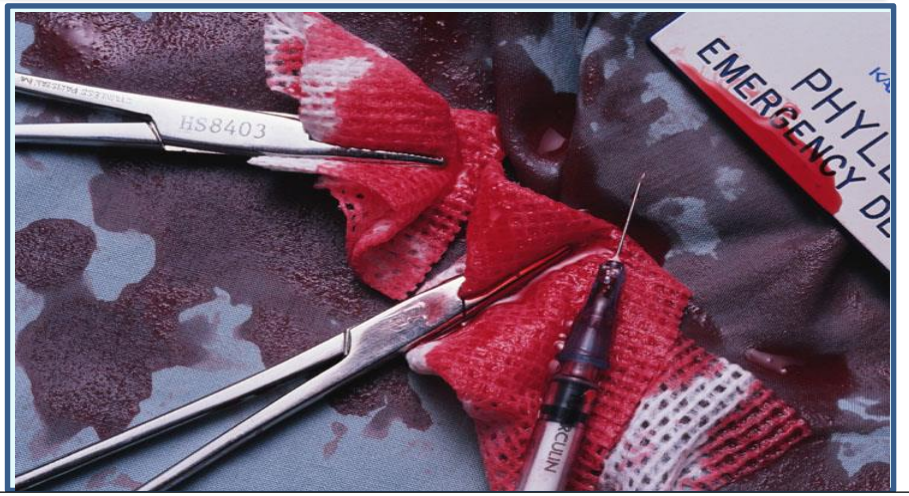
Grant PI: Donald Jenkins **Study PI:** Henry M Cryer **Org:** UCLA **Award Amount:** $499,995

Study/Product Aim(s)

- Determine the shelf life of FWB
- Prospectively determine the effectiveness of trauma resuscitation using FWB compared to component therapy
- Test the feasibility and implementation of a system to provide FWB for resuscitation of trauma patients in hemorrhagic shock

Approach

After determining the shelf life of FWB, by measuring coagulation markers, trauma patients in hemorrhagic shock presenting to the ED will either receive component therapy or whole blood resuscitation. Blood samples, collected from time of presentation until 7 days after admission, will be analyzed and compared for markers of inflammation and coagulation. Clinical data, including blood transfusion requirements, development of coagulopathy, venous thromboembolism, infections, and mortality, will be collected and compared prospectively.



Non-filtered FWB stored at 4C retains functional global clotting capacity for up to 35 days, suggesting that FWB leukoreduced with a platelet-sparing filter, stored for prolonged periods of time, will be an acceptable stand-alone product for resuscitation from hemorrahagic shock.

Timeline and Cost

Activities CY	15	16	17
Determine the shelf life of FWB		$250	
Determine the effectiveness of trauma resuscitation using FWB compared to component therapy		$150	
Test the feasibility and implementation of a system to provide FWB for resuscitation of trauma patients in hemorrhagic shock			$100
Estimated Budget ($K)	**$250**	**$150**	**$100**

Updated: (09/22/17)

Goals

CY15 Goals – Determine the shelf life of FWB

☐Measure coagulation markers in stored FWB

☐Analyze data from in vitro study

☐Begin community consent process to get IRB and DoD approval for clinical study (Not longer necessary)

√ Get IRB approval for the clinical study

CY16 Goal – Begin clinical study

☐Establish rolling inventory of banked whole blood

☐Enroll patients in control and experimental arms of the study

☐Measure coagulation markers in patient samples

CY17 Goal – Complete clinical study; Test feasibility of a system to provide for resuscitation of trauma patients in hemorrhagic shock

☐Analyze clinical sample data

☐Analyze data regarding whole blood utilization and cost